Chapter 14
Cellular and Molecular Basis of Regional Anesthesia and Acute Pain Practice and Applications to Personalized Medicine

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Introduction

Personalized Medicine

Personalized, or precision, medicine describes an approach to disease prevention, diagnosis, and treatment that seeks to maximize treatment effectiveness and minimize unintended or adverse effects by incorporating an individual's variability in genes, environment, and lifestyle in a sophisticated data-driven manner (Ginsburg and Willard 2009).

Over the last few decades, there has been an explosion in genomic, molecular, and cellular biology data combined with advances in medicine which stand to revolutionize health care treatments and outcomes. Genetic data can be used to better design a study or to identify the subgroup of patients who may obtain the maximum benefit from a treatment with minimal toxicity. This also changes how health and disease is classified. To this end, the National Academy of Sciences committee published a framework for integrating genomics, proteomics, metabolomics, and other data sources into a new taxonomy disease which naturally gives way to personalized medicine (National Research Council Committee on 2011).

This step forward in medicine has only recently been possible with advances in areas like molecular biology, novel biomarker identification, high throughput drug

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development, cost reductions in sequencing, and data science alongside electronic medical records which establish meaningful relationships with longitudinal analysis.

While personalized medicine can be broken down in various ways, recognized principal areas are:

1. Genomic medicine, which refers to defining penetration of different genetic mutations and pharmacogenomics
2. Molecular medicine, which is related to the molecular-based mechanism of disease and therapeutics
3. Data Science, which might include risk stratification and the application of electronic health records (EHR) and genomics for prediction of a pathologic state
4. Implementations Science, which integrates the domains of precision medicine, genomic and biomarker data in the healthcare setting (Table 14.1).

The tools of precision medicine, or resources that are incorporated include:

1. DNA array genomic, genotyping and sequencing of disease state
2. Correlating the pathologic states with biobanks
3. Electronic health records with other digital technologies
4. Big data methods and machine learning with artificial intelligence
5. Phenotyping
6. Large multicenter clinical trials.

While still a burgeoning medical discipline, there are many areas where personalized medicine is currently being used, perhaps most notably within medical oncology where an individual's tumor genetic mutation profile can be sequenced and used for precise therapeutic targeting (Papaemmanuil et al. 2016; Grinfeld et al. 2018; Schmitz et al. 2018). Precision medicine may also find an impact in areas of medicine like psychiatry where treatments are often trial-and-error through classes of medications while pharmacogenomics could tailor empiric treatment (Ozomaro et al. 2013; Torres et al. 2016).

Another area where personalized medicine is being realized is in the identification and validation of new targets in drug developments through accurately modeling cellular and molecular interactions. Incorporating genetically-supported targets allows for designing and tailoring novel therapeutics (Dugger et al. 2018). Large computational workflows that incorporate next-generation sequencing, functional

Table 14.1 Resources of personalized medicine

Category	Definition
Genomic medicine	Defining penetration of different genetic mutations and pharmacogenomics
Molecular medicine	Molecular-based mechanism of disease and therapeutics
Data science	Application of electronic health records (EHR) and genomics for prediction of a pathologic state
Implementations science	Integrates the domains of precision medicine, genomic and biomarker data in the healthcare setting

proteomics, and molecular network analysis could comprehensively overhaul our approach to discovering new medicines (Lippmann et al. 2018).

One of most exciting area of precision medicine is in using genomics to build a genetic risk score (GRS) model for predicting disease and treatment response. The GRS model has been used in coronary heart disease (CAD) in select epidemiological cohorts. For instance, a population with high GRS for CAD may benefit from statin therapy (Mega et al. 2015). This approach to treatment represents a turn from clinical heuristics, or decisions based on rudimentary divisions or flow charts derived from limited studies, to real-time data-driven risk profiles and therapeutic recommendations.

Toward this future care model, the NIH through the National Human Genome Research Institute created the Electronic Medical Records and Genomics (eMERGE) network to fund cross-institutional research combining biorepositories with EHR systems for genomic medicine (McCarty et al. 2011) which aims to "develop and validate electronic phenotyping algorithms for large-scale, high-throughput genomics research." Other public consortiums are also collecting and integrating pharmacogenomic data such as PharmGKB (Whirl-Carrillo et al. 2012).

Personalized Medicine in Regional Anesthesia

There are many potential future applications of personalized medicine within the field of Anesthesiology. This chapter focuses on exploring that topic with regard to perioperative pain management using regional anesthesia, an established and growing subdiscipline that focuses on the relief of perioperative/surgical pain primarily through the inhibition of nerve transmission. Good pain management in the perioperative setting does more than relieve the inconvenience of pain, it reduces the body's stress response to surgery which has many benefits, such as even reducing the risk of post-op MI (Beattie et al. 2001).

The goal of this chapter is to discuss principles of regional anesthesia and its potential applications in personalized medicine by exploring the genomics of pain, basis of nociception and peripheral nerve anatomy, the cellular/molecular mechanisms of local anesthetics, and the role of regional anesthesia in surgical oncology.

Personalized medicine within regional anesthesia is still very new with much left to speculation at this juncture. It is likely that pharmacogenomics will be a small aspect of personalized regional care.

Brief History of Regional Anesthesia

The purpose of regional anesthesia is to eliminate pain through the direct inhibition of nerve transmission. By stopping the noxious signal, we can eradicate the sensation of pain and limit the sympathetic response to injury. This signal intervention

can be through basic tissue infiltration, perineural injections, or neuraxially at the level of the spinal cord. The role and specificity of regional anesthesia has greatly expanded with our understanding of nerve anatomy and physiology, molecular basis of nociception, and real-time targeting ability through ultrasound.

Before the discovery of local anesthetics (LA), the only means to establish a peripheral nerve block were direct compression of the nerve or the application of ice which were ineffective and prone to injury. While the full history of regional anesthesia can be gleaned from more comprehensive sources, it helps to have a perspective which we will outline here.

Regional anesthesia had its advent in the late nineteenth century with the discovery of local anesthetics, the first of which being cocaine, an extract of coca leaves long known to produce a numbing sensation when chewed on (along with its more notorious stimulant effects). Ether had only been recently discovered, but already general anesthetics were decidedly not ideal in dentistry and for certain surgeries, especially when emergence followed with retching.

While there were many scientists, dentists, and physicians involved in the research of cocaine as a topical anesthetic, the first recognized use occurred in 1884 by Koller (Calatayud and González 2003) who administered topical cocaine for ophthalmologic surgery, a procedure that benefits from an awake, directable patient. Along with the invention of the hypodermic needle and syringe, cocaine was soon expanded from topical use to skin infiltration, peripheral nerve blockade, and the first spinal and epidural injections—each method discovering its effective dose, toxicity, and, unfortunately for cocaine, dependence. While intravenous injection proved to be short-lived as a regional technique, Bier introduced a tourniquet that prolonged its duration still in use today.

Cocaine was the exclusive local anesthetic for around 20 years until the synthesis of amylocaine (Stovaine) in 1903 and procaine (Novocain) the following year. Lidocaine, the best known and most used local anesthetic, was not introduced until around 1947. By then, scientists recognized the helpful categories of local anesthetics based on whether they had an amide or ester bond, with the esters having worse shelf-life, duration of action, and the occasional allergic reaction to the otherwise non-toxic by product para-aminobenzoic acid (PABA). Research focused on developing amide anesthetics with mepivacaine and bupivacaine introduced in the 1960s. Modifications and enantiomer separation led to ropivacaine and levobupivacaine introduced in the 1990s as less cardiotoxic alternatives to bupivacaine. Research continues in synthesizing novel local anesthetics.

Regional anesthesia as a field has markedly evolved as well. As our understanding of spinal and peripheral nerve anatomy advanced, so did the neuraxial and peripheral block techniques. Landmark based nerve localization developed in conjunction with nerve stimulators and were used for most of the twentieth century, often requiring large injectate volumes and passing the needle through large arteries. These days, ultrasound has greatly increased the precision and targeting of peripheral nerves, affording a durable block with lower injection volumes and lower risk of nerve injury.

Regional techniques have been established as a preferred anesthetic when possible. In the ASA Practice Guidelines for Acute Perioperative Pain Management (2012), regional approaches conferred improved pain scores across studies and when polling anesthesiologists, 95% agreed or strongly agreed that a regional block should always be considered with multimodal pain management.

Principles of Pain Transmission

Peripheral nerves carry sensory input, motor output, and sympathetic innervation. In general, local anesthetic agents act most potently on sympathetic nerves followed by sensory nerves and finally motor nerves. This variable effect leads to what is known as a differential blockade. Much of this can difference be explained by the respective nerve properties which are: fiber type, diameter, conduction, and myelination. The local anesthetic choice also plays an important role in the degree of differential block (Gissen et al. 1980; Rosenberg and Heinonen 1983). Fiber types are categorized by their average diameter using the Erlanger-Gasser classification of A, B, and C with A having subtypes α, β, γ, and δ. Type A are myelinated with the largest diameter and fastest conduction while "type C" are unmyelinated with the smallest diameter and slowest conduction velocities.

Primary sensory neurons, the first order afferent input, have their cell bodies in the dorsal root ganglion (DRG) with a distal axonal extension to the skin periphery and the other end synapsing in the dorsal horn of the spinal cord. Sensory input is delivered via Aβ, Aδ, and C fibers. Aβ fibers compose light touch and pressure, Aδ compose pain (fast) and temperature, and C fibers carry the largest population of nerves relaying pain.

When primary nociceptors are activated, the sensory neurons release a cascade of molecules at their synapse in the spinal cord including Substance P (SP), calcitonin gene-related peptide (CGRP), and glutamate. The sensory neurons also release molecules at their peripheral terminals including SP which acts through the Neurokinin 1 receptor (NK_1) causing vasodilation and local inflammation. There are also many local signaling molecules that can influence the activity of nociceptor fibers.

Much of the research on inflammatory pain states have shown that C fibers have receptors for many cytokines such as TNF-a, IL-1b, and IL-17 (Schaible 2014) that can induce sensitization through upregulation of TRPV1, a non-selective ion channel which is responsible for transducing thermal and mechanical pain. This channel is also known to be activated by capsaicin. There is ongoing research into TRPV1 and NK_1 receptor antagonists to counteract this sensitization which may find use within regional anesthesia for patients with chronic pain states. Perhaps measuring an individual's cytokine expression profile could aid in identifying personalized regional treatments when patients undergo surgery.

Individual Differences in Response to Pain/Perioperative Pain Genomics

Although tissue damage and activation of pain receptors is the first step in the cascade of noxious stimulation, the degree of pain for the same insult varies significantly between subjects, thus important and inseparable part of a pain phenotype is to show the individual variability and difference in sensitivity. Pain sensitivity measurements largely derive from animal models given the controlled setting. There is substantial evidence that pain sensitivity in these experimental measures is related to degree of pain, however, lack of control over degree of noxious stimulus is a considerable limitation of these studies (Verne et al. 2001; Carli et al. 2002; Petzke et al. 2003; Giesecke et al. 2004a, b; Staud 2010).

On the other hand, using electronic medical health records to gather large and heterogeneous population based data with wide and diverse pain sensitivities may overcome the discrepancies across types of pain. One may assume that different pain phenotypes may have one underlying dormant hidden phenotype supported by multiple single-nucleotide polymorphisms (SNPs). This approach has been used in twin studies where the hidden phenotype explained 95% risk of developing pain in separate parts of body (Williams et al. 2004).

In the situations where the pain condition does not involve a clear tissue pathology, or idiopathic/dysfunctional pain, the presence of many environmental contributors affect the pain phenotype significantly, with phenotypic changes as the disease progress (Linnman et al. 2011).

Most pain syndrome phenotypes are complex, and their inheritance do not follow the Mendelian patterns. However, research in rodents and human twin studies have shown considerable invertibility of nociception, clinical pain syndromes, sensitivity to pain, and response to analgesics (Diatchenko et al. 2006; Fillingim et al. 2008; Lacroix-Fralish and Mogil 2009; Angst et al. 2012; Mogil 2012). As expected, though, animal models don't reliably predict human responses to pain.

Interestingly, genetic influences on pain intensity can differ considerably based on the gender of the individual and the level of stress associated with the pain condition. There is evidence, for instance, that female gender is associated with more postoperative pain (Fillingim et al. 2009; Ruau et al. 2012b). A study using EHR on more than 11,000 patients showed that women report higher pain scores compared to men following similar diagnostic procedures (Ruau et al. 2012b). Using a mouse model, XX genotype and gonadectomized mice showed greater thermal and chemical nociceptive sensitivity and greater morphine resistance than XY mice. Whereas in the presence of gonads, XX mice showed more tolerance to morphine (Gioiosa et al. 2008). The relation to gonadal hormones, especially estrogen receptor genes on the pain intensity and analgesic responses has also been demonstrated (Craft et al. 2004). In a transgenic mice model, estrogen beta receptors (ERβ) demonstrated a pro-nociceptive role in both sexes (Coulombe et al. 2011). Using quantitative trait locus mapping (QTL)—a technique in which a trait gene can be located by using inheritance patterns, *Calca* or calcitonin gene-related peptide (CGRP)

encoding gene, was identified as a major genetic predictor for thermal nociception in mice and potentially humans. *Calca* is much higher in female mice than male (54 vs. 36% respectively) (Mogil et al. 2005).

However, studies on human pain genetics regarding gender associations are contradictory. For example, the A118G SNP opioid receptor Mu 1 (OPRM1) gene has been associated with more pressure-pain sensitivity in females than males (Way et al. 2009). COMT (Catechol-*O*-methyltransferase) genes were associated with higher pain scores in females but not in males (Fijal et al. 2010). In contrast, actin-binding LIM protein 3 gene is associated with cold-induced pain in males and not females (Ruau et al. 2012a). A study by Aoki showed that the serotonin 2A receptor gene (5-HTR2A) is associated with more analgesic requirements in women following abdominal surgery than men.

The effect of physical and psychological stress on pain related syndromes are well known. Stress as a factor for modulating pain can enhance or diminish pain sensitivity, therefore stress can cause stress-induced hyperalgesia or stress-induced analgesia (Imbe et al. 2006; Butler and Finn 2009). The presence of COMT variants has been shown to predict pain and psychological symptoms after motor vehicle collisions with the associated physical and psychological stress (McLean et al. 2011). Another study looking at SNPs in COMT showed that a homozygous variant group consumed almost 40% more opioids than their counterparts (Candiotti et al. 2014). However there are many more genes that relate to pain, opioid responses (Ren et al. 2015; Li et al. 2019) and experience even including immune cell Toll-like receptors with at least 640 genes found to date that play a role in the experience and modulation of pain (Liu et al. 2012; Peirs and Seal 2015; Bagheri et al. 2016; Sezari 2017; Lippmann et al. 2018; Zali et al. 2019).

Organization and Ultrastructure of the Peripheral Nervous System

Histology and Electron Microscopy of Human Peripheral Nerves System

In the last few decades, the detailed structure of the peripheral nervous system has been shown through anatomic dissections with histological and electron microscopy. The electron microscope has added more detailed information on the ultrastructure and histological details of the peripheral nervous system. Some of the highlighted details of this ultrastructure may be meaningful to the future practice of peripheral nerve blocks.

The peripheral nervous system (PNS) includes neurons with various functions, somatic and autonomic. The basic functional unit of the nervous system is the neuron. Neurons are supported by other nervous system cells called neuroganglia. Each neuron is composed of a cell body, dendrites, and a single axon.

The *cell body* or *soma* or *perikaryon* is the most conspicuous part of a neuron and usually with a prominent spherical or ovoid nucleus. The neuron cytoplasm includes rough endoplasmic reticulum (RER) with many cisternae and polyribosomes. When polyribosomes attach to the RER, they produce *Nissl bodies*, which are even visible with a light microscope. In the axon hillock, the region of soma from which axon rises, smooth endoplasmic retinaculum (SER) replaces the RER. Another prominent part of cell body is the *Golgi apparatus*, the protein secreting part of the cell and in charge of neurotransmitter packing. Numerous mitochondria are scattered in the cytoplasm and even more abundant at axon hillock. Electron microscopic details of cytoskeletal components reveal three different filamentous structures: microtubules (up to 24 nm diameter), neurofilaments (10 nm diameter) and microfilaments (6 nm diameter).

Axons are the cellular projections that run from a source to target by conducting current. These axons are arranged in a hierarchical manner with groups of efferent motor axons, afferent sensory axons, and sympathetic fibers.

Electron microscopic examination of myelinated axons has shown that each axon has a very dense cytoplasm with mitochondria, microtubules, lysosomes, neurofilaments, cisterns of cytoplasmic reticulum and cytoplasm.

Axons start from axon hillock as a single thin process and can be extended over a meter. Axon thickness directly correlates with its velocity, or that the diameter increases as current velocity increases. *Axoplasma* or cytoplasm of an axon is a very thin and dense layer. This area of axon has no RER but has numerous microtubules and neurofilaments.

The axons can be divided into myelinated and unmyelinated. Neuronal axons are myelinated by *Schwann cells* which run along the nerve tracts and wrap the axon in a myelin sheath (Fig. 14.1). All the motor neurons and some sensory neurons are myelinated.

Schwann cells are only located in the PNS. They are flat cells including a flattened nucleus. Electron microscopy has shown that myelin is actually the plasmalemma of the *Schwann cell* that is wrapped several times around the axon. Interruption of this sheath occurs at points along the axon called *nodes of Ranvier* which are the interface between two adjacent *Schwann cells*. Each *Schwann cell* and its associated nodes of Ranvier is covered by a basal lamina. The basal lamina functions as the regenerative guide following nerve injury. *Schwann cell* cytoplasm can be trapped into the lamellae of the myelin creating a cone-shaped cleft in the myelin sheath of each internodal segment known as a *cleft of Schmidt-Lanterman*. Narrow outer leaflet of *Schwann cell* plasma membrane is call *intraperiod line*. High resolution electron microscope has shown small gaps in this line between layers of myelin which is called *intraperiod gaps*. The gaps are potential access for small molecules to reach the axon.

Unmyelinated axons are not covered with myelin sheath but 6–8 of unmyelinated axons can be associated with one *Schwann cell* that separates these axons from each other. Although sometimes one unmyelinated axon may be surrounded with one single layer of *Schwann cell* (Fig. 14.2) (Chen et al. 2011; Reina et al. 2013).

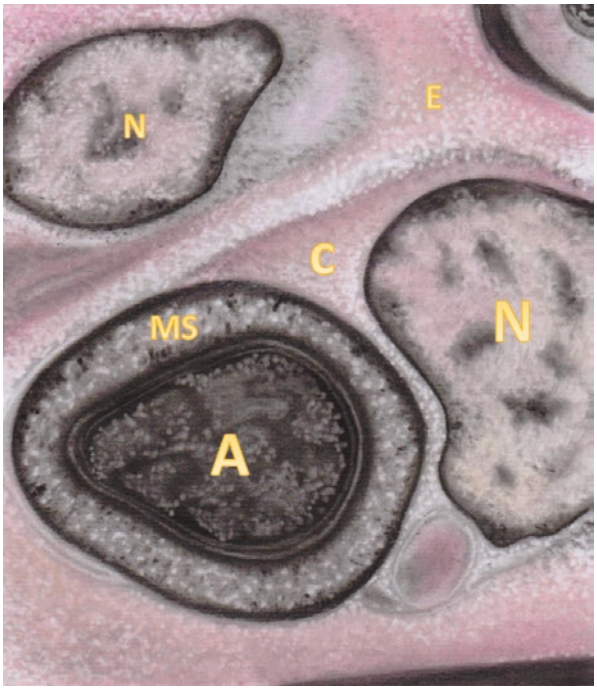

Fig. 14.1 Graphic image of an electronic microscopic picture of myelinated axons (A) with Schwann cells (C) wrap around the axon. MS: Myelinated Sheaths, A: Myelinated Axon, N: Schwann cell Nucleus, E: Endoneurium C: Cytoplasm of Schwann cell

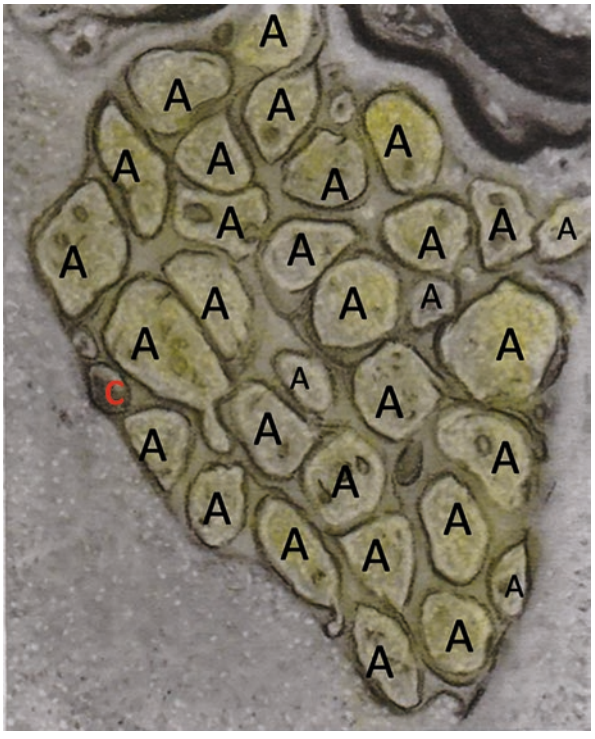

Fig. 14.2 Graphic drawing of an electron microscope image of an unmyelinated axons (A). A group of unmyelinated axons may accompany with a Schwann Cell (C)

Synapses

Synapses are the sites where nerve currents are transmitted from a neuronal source (presynaptic) to ass receiver (postsynaptic) neuron, muscle cell, or gland cell. At each synapse, the presynaptic neurons form a bulbous expansion at the end of an axon or dendrite called the *bouton terminal* or *boutons en passage*. Different types of synapses are explained in Table 14.2.

The cytoplasm at the presynaptic membrane contains SER, many synaptic vesicles and many mitochondria. Synaptic vesicles are oval, 40–60 nm in diameter, and contain neurotransmitters to be released. Cell membrane close to a synapse has a cone-shape projection toward the postsynaptic membrane and forms the active side of the synapse where the vesicles are released. Synapsin I is a complex protein that helps to hold the synaptic vesicle in the active site. Phosphorylation of this protein determines the transmission direction. Synapsin II is another protein which controls the vesicles with microfilaments. Other synaptic proteins that help unloading neurotransmitters are synaptotagmin and synaptophysin.

The postsynaptic membrane is a thickened portion of receiving cell membrane which contains the neurotransmitter receptors.

Peripheral Nervous System

Peripheral nerves are composed of bundles of nerve fascicles extended outside of the CNS. The nerve fascicle is the functional unit of a nerve and consists of a group of axons covered by *endoneurium* and packed within another layer, the *perineurium*.

Endoneurium is the innermost layer of connective tissue that surrounds each axon and Schwann cell. *Endoneurium* is composed of reticular fibers, macrophages, capillaries, mast cells and fibroblast cells and serves as a separation compartment of each nerve.

Perineurium covers each bundle of nerve fascicles and is composed of a thin connective tissue with several layers of epithelioid cells joined together by *zonulae occludentes* and basal lamina. This layer is an isolation layer which is also called *blood-nerve barrier*.

Epineurium consists of connective tissue and vessels which cover all of the fascicles. *Epineurium* is composed of dense, irregular and collagenous connective tissue. This layer becomes thinner as nerves branch to more distal and smaller nerves.

Table 14.2 Types of synapses

Name	Type
Axosomatic synapse	Synapses between axon and a soma
Axoaxonic synapse	Synapses between two axons
Axodendritic synapse	Synapses between axon and dendrite
Dendrodendritic synapse	Synapses between two dendrites

Microanatomy and Interneural Topography of Brachial Plexus

Microscopic examination of the brachial plexus has shown significant differences and complicated structure in histologic appearance from the interscalene region to the axilla. The level of the cords, the nerve elements are relatively isolated. However, bifurcation and recombination of the fascicles happen at the level of the trunk. As the brachial plexus progresses toward more division and cords, the number of fascicles increase and spread into a wider space (Fig. 14.3) (Chen et al. 2011).

Microanatomy and Interneural Topography of Sciatic Nerve

Topographic maps of the sciatic nerve showed that this nerve and its branches vary. This variability is due to exchange of axons which start at the level of the dorsal root and continue along the main trunk. Number of nerve fascicles also increases along the course of the nerves (Sunderland and Ray 1948) (Fig. 14.4). Sciatic nerve at the level of popliteal fossa is supported by perineurium in connection to epimysium, whereas each group of fascicles is mainly filled with fat and collagen tissue.

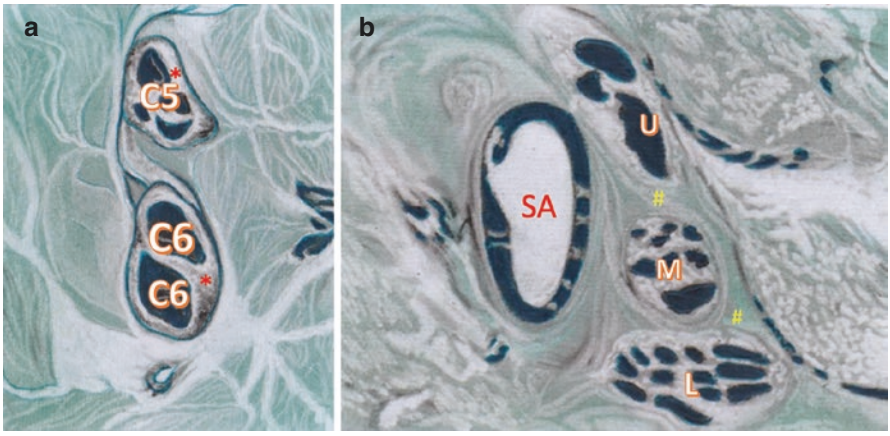

Fig. 14.3 Schematic image of the difference in appearance of brachial plexus at the C5 and C6 roots (**a**) and Trunks (**b**) – At the level of the trunks more prominent perineurium (*) tissue is noticed whereas at the level of the trunks more interstitial tissue and adipose (#) tissue fills the intertruncal planes. U: Upper Trunk, M: Middle Truck, L: Lower Trunk, SA: Subclavian Artery

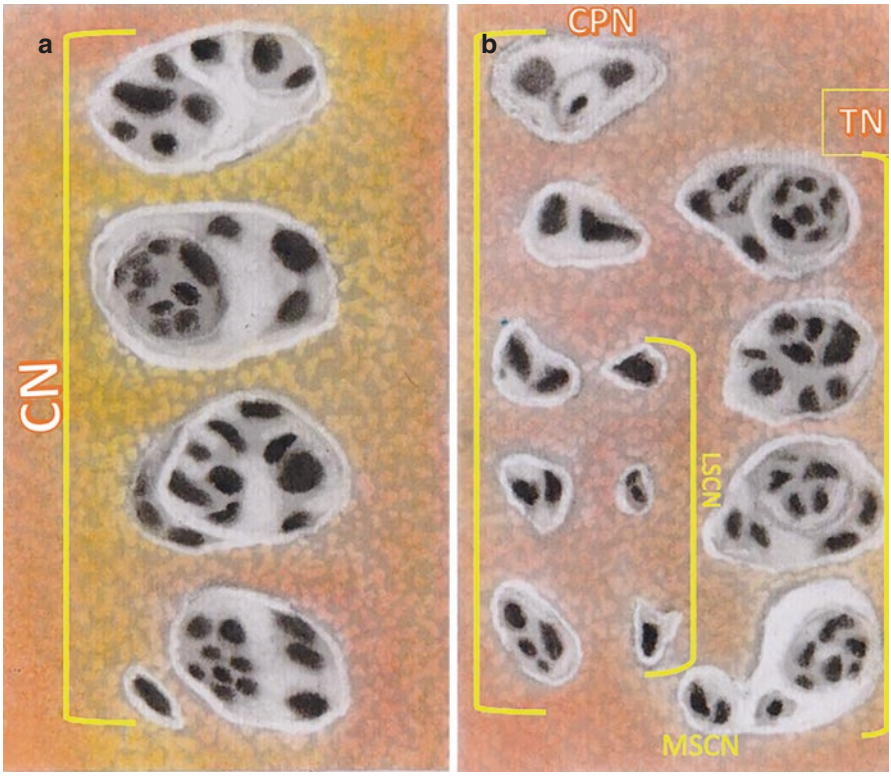

Fig. 14.4 Graphic image of the cross-sectional histology of A- human sciatic nerve (CN) and B- its branches in their course from the popliteal fossa to proximal leg. Common Peroneal Nerve (CPN), Tibial Nerve (TN), Lateral Sural Cutaneous Nerve (LSCN) and Medial Sural Cutaneous Nerve (MSCN)

Molecular Basis of Regional Anesthesia

Local Anesthetics

Local anesthetics (LA) are the primary pharmacologic category used in regional anesthesia as they induce complete, reversible interruption in nerve transmission.

Local anesthetics consist of hydrophilic (amine) and hydrophobic (aromatic ring) ends linked by an ester or amide bond. The type of bond divides the two classes of LAs as it reflects their metabolism. Amino esters are rapidly metabolized by plasma pseudocholinesterases while amino amides are metabolized by the liver cytochrome P450 system, generally CYP3A4 and CYP1A2 (Oda et al. 1995; Wang et al. 2000).

The amine group on LAs make them weak bases which at physiologic pH predominate in a protonated amine/charged form that cannot penetrate cell membranes.

Uncharged forms however readily cross cell membranes to their site of action. Each LA has its own pKa, usually around 8–9. As the pKa decreases, the speed of onset increases as a higher proportion will be in its diffusible, uncharged form. The aromatic ring can additionally host lipophilic R-groups that increase its potency so that it passes more easily through neuronal membranes allowing lower concentrations to be used (Becker and Reed 2012). The duration of a block generally relates to its degree of protein binding and the inclusion of a vasopressor such as epinephrine that limits local clearance.

In other words, local anesthetics can be engineered to have specific onset, duration, and potency. However, such modifications can have other effects such as the amount of local vasodilation, degree of differential block, and toxicity profile. The worst complication of local anesthetic systemic toxicity (LAST) is complete cardiovascular collapse that is heralded by convulsions. Fortunately, this complication is exceedingly rare. In an 8 year study on 12,668 patients receiving peripheral nerve blocks there was 1 seizure and 0 cardiac arrests (Sites et al. 2012). One way to limit the absorbed dose and prolong the block is through new delivery vehicles such as with liposomal bupivacaine (Malik et al. 2017).

Local anesthetics act on voltage-gated sodium channels (VGSC). VGSCs are densely populated along the entire length of unmyelinated axons and concentrated at nodes of Ranvier in myelinated axons. The VGSC exists in 3 conformational states: activated/open, inactivated, and resting/closed. LAs bind the cellular side inner pore in domain IV S6 of the channel during depolarization, leading to what is known as a state-dependent block (Strichartz 1976; Fozzard et al. 2011). When open, the channels allow sodium ions to flow down their concentration gradient propagating an action potential which is blocked by local anesthetic binding.

There are 9 VGSC isoforms in humans, regulated and expressed by tissue type and divided into tetrodotoxin sensitive and resistant (Novakovic et al. 2001). The full functional structure of VSGCs are still being elucidated, but as our understanding of theses intricate ion channels improve, we may be able to engineer new drugs that antagonize the receptor at unexplored binding sites (Lai and Jan 2006), perhaps in combination with local anesthetics that work synergistically at significantly lower doses. There are even proposals to create channel isoform specific antagonists for controlling syndromes like chronic cough (Muroi and Undem 2014).

Outside of action on VGSC, local anesthetics have both demonstrated and postulated roles in other pathways and receptors such as on protein kinases, calcium signal modulation, and G-protein coupled receptors (Nivarthi et al. 1996; Hollmann et al. 2001; Xu et al. 2003).

Current dose limits for local anesthetics to mitigate risk of toxicity tend to be overly conservative and not empirically based with data derived from single clinical events and animal data (El-Boghdadly et al. 2018). Furthermore, the site of LA injection has a large influence on the rate of uptake and peak plasma concentration (de Jong and Bonin 1980). Combined with differences in liver metabolism, drug-drug interactions, and ion channel genetic variations, there are many variables that can influence peak plasma concentration. Even what concentration causes side

effects is unclear. Perhaps one area of personalized regional anesthesia will be in establishing local anesthetic maximum doses.

One interesting area of research with novel local anesthetics is investigating charged quaternary ammonium LAs such as QX-314. While charged molecules take a long time to cross the neuronal membrane, there is nevertheless a slow onset but long lasting effect with them (Lim et al. 2007). Even more intriguing, in combination with capsaicin QX-314 can produce a sensory specific block. The TRPV1 receptor can be found on C pain fibers and activates in response to capsaicin. One group demonstrated that performing a block in animals with QX-314 followed by capsaicin 10 min later at the same site produced a dense sensory specific block. The hypothesis is that the TRPV1 receptor activation facilitates entry of QX-314 into the cell where it is able to have a fast and sensory specific onset (Gerner et al. 2008). Further analysis of membrane proteins and channels throughout peripheral nerves will further refine the ability of regional anesthesia to target nerve types precisely.

Adjuvants

While local anesthetics are the principal drug used in regional anesthesia, there is ongoing research on the utilization of adjuvant medications for use in peripheral and neuraxial blocks. Local anesthetics have a limited duration of action and dose dependent adverse events. Adjuvants have been used to synergize the effect and prolong block duration. Epinephrine is the most familiar co-administered drug with LA which causes vasoconstriction that limits systemic absorption. Another class of medication used to facilitate regional anesthesia are α_2 agonists such as clonidine or dexmedetomidine. There have been trials with many classes of medications with varied results including steroids, anti-inflammatory agents, ketamine, benzodiazepines, and even neuromuscular blockers (Swain et al. 2017).

Role of Regional Anesthesia in Oncology

As we have come to understand, surgery and medications used in anesthesia can have profound effects on the function of the immune system. This is particularly relevant in surgical oncology. Studies have shown that there are many perioperative factors that can contribute to immune suppression such as the stress response, opioids, volatile anesthetics, blood transfusions, hypothermia, and inadequate pain control. Surgery itself is associated with decreased immune function due to pain, stress, and tissue damage, and can even trigger metastases as first demonstrated in mice (Shapiro et al. 1981; Kurz et al. 1996; Page 2005; Stollings et al. 2016; Tohme et al. 2017).

Recurrence and spread are particularly worrisome because the introduction of tumor cells into circulation depends on host defenses, specifically natural killer (NK) cells and macrophages, as the primary immune cells against cancer. Multiple perioperative factors help limit the degree of spread and recurrence. Factors that can

accelerate the spread of cancer include shedding of the cells into the blood and lymphatic system at the time of tissue trauma, increasing cancer cell growth factors such as TGF-β and catecholamines, and increasing pro-angiogenic factors such as VEGF. The surgery itself induces a neuroendocrine response with the release of several cytokines. In the early phase of cell trauma, there is a release of pro-inflammatory cytokines including IL-1, TNF-α inducing a leukocytosis. In the latter phase, depression of both acquired and innate immune function predispose the patient to sepsis, nosocomial infections, and tumor growth (Denstaedt et al. 2018).

Fortunately regional anesthesia has emerged as a potential factor that can mitigate the degree of immune suppression by reducing the stress response and the need for post-operative opioids which themselves can inhibit innate and adaptive immune function (Sacerdote et al. 2000). Spinal anesthesia in patients who undergo transurethral resection of the prostate has been shown to increase T-helper 1 (Th1) cells which produce interferon and support cell-mediated immunity with T-helper 2 (Th2) cells which produce IL-4 and propagate the humoral immunity improved compared to patients who undergo the same procedure under general anesthesia (GA) (Le Cras et al. 1998).

Wada et al., also showed that addition of addition of spinal anesthesia to GA attenuates the suppression effect of GA on tumoricidal function of the liver mononuclear cells, presumably by preserving the Th1/Th2 balance and thereby reduces the promotion of tumor metastasis (Wada et al. 2007). One study on using a paravertebral block (PVB) after breast cancer surgery also showed that a PVB led to greater natural killer cell activity compared to those who had GA which may affect recurrence or metastasis (Exadaktylos et al. 2006; Gottschalk et al. 2010; Buckley et al. 2014). Combination of epidural analgesia with GA has also been shown to reduce the change of cancer recurrence in patients with prostate cancer (Exadaktylos et al. 2006). However it was controversial to show any effect on recurrence of colorectal cancer (Gottschalk et al. 2010; Cummings et al. 2012).

Going further, a retrospective study of patients undergoing resection for head and neck cancers compared cervical epidurals with GA to GA alone and showed that the 5 year survival was higher in the group with an epidural (68% compared to 37%). Another retrospective study of 50 women undergoing mastectomy for breast cancer compared GA with or without a paravertebral block, showed that recurrence and metastasis free survival at 36 months was 94% in the paravertebral group and 77% in the general anesthesia only group (Exadaktylos et al. 2006). Another retrospective study compared GA with and without an epidural in patients undergoing radical prostatectomy, the epidural group had a 57% lower risk of cancer recurrence compared with general anesthesia with opioids (Biki et al. 2008). Generally, when things sound too good to be true, they are, and in fact a recent randomized controlled study by Sessler, et al. looked at 2132 women undergoing surgery for breast cancer comparing PVB with GA with regard to cancer recurrence and did not show significant differences in survival or recurrence (Sessler et al. 2019).

Another area of influence in oncology is the chemotherapeutic effects of local anesthetics. In vitro, lidocaine has been shown to enhance NK cells via the release of lytic granules (Ramirez et al. 2015).

Chronic inflammation can induce DNA damage and is thought to contribute to 25% of cancers (Kawanishi et al. 2017). Increased tumor multiplicity secondary to hormonal mediators such as Src tyrosine protein kinase, which is involved in inflammatory signaling, has been shown to have a crucial role in solid cancer metastasis (Meira et al. 2008). Src tyrosine protein kinase is involved in signaling epithelial cell to mesenchymal transformation, promoting cell survival and mitogenesis and has significant effect on the cytoskeleton remodeling for cell migration necessary for tumor metastasis (Liu et al. 2013). Intercellular Adhesion Molecule 1 (ICAM-1) is a surface glycoprotein which is typically expressed on endothelial cells and cells of the immune system. Increased level of ICAM-1 is associated with an aggressive tumor expression. In addition, ICAM-1 expression is associated with a reduction in the disease-free interval in patients with liver metastasis, breast cell carcinoma, and gastric cancers (Kageshita et al. 1993; Maruo et al. 2002; Rosette et al. 2005).

The effect of amide linked local anesthetics on the non-small cell lung cancer (NSCLC) NCI-H838 lung cancer cells showed that ropivacaine and lidocaine decease ICAM-1 phosphorylation and Src activation in a dose-dependent manner (Piegeler et al. 2012). The effect of ropivacaine and lidocaine on the migration of NSLC cells was also inhibitory. However, these effects has not been observed with ester linked LAs. Intravenous lidocaine can also suppress inflammatory mediators such as IL-1 which indirectly helps immune function (Yardeni et al. 2009).

In summary, regional anesthesia and prevention of the inflammatory response can enhance immunity and prevent cancer expansion. Local anesthetics, especially amide based, have a direct effect on the modulation of the immune system and attenuate inflammatory responses. Although these effects may have beneficiary effects on the recurrence of cancer metastasis, further clinical studies are needed to clarify these findings.

Electronic Health Records and Machine Learning in Regional Anesthesia

Roughly 97% of US hospitals have reported using longitudinal records of patient medical and health history over the last 15 years. The role of EMR systems in changing health care cannot be overstated. Outside of its early goals of reducing errors, redundancies, cost containment, and compliance, one of the evolving benefits is clinical decision support and automation using passive or active support pipelines for enhancing clinical competency with regard to diagnosis and treatment plans (Appari et al. 2012, 2014; Rothman et al. 2012; Kharrazi et al. 2018).

Combining and linking the EMR with biobanks has created wide data rich networks such as eMERGE which includes records of 8.9 million patients with 600,000 cases of psychiatric disorders and genomic data up to 254,000 (McCarty et al. 2011).

This vast and continuously growing data can be too sparse and multidimensional to be wielded by simple hypothesis driven logistic regression. Instead large-scale analyses can be performed by machine learning. As machine learning algorithms

and natural language parsers become increasingly sophisticated and independent without model training, the developed AI will be able to perform real-time diagnostic and therapeutic risk estimates far exceeding today's capabilities.

Machine learning in regional anesthesia and pain medicine has already started to penetrate the field as a fast growing topic. It has been used to predict need for femoral nerve block after ACL repair or to predict requests for preoperative acute pain service consultation (Tighe et al. 2011, 2012a, b, c). Integrated data from ICUs, labs, and clinic notes to are also used to predict length of hospital stays and clinical needs (Gardner 2016).

EMRs combined with GRS may provide even more precision in prediction models. Some of the top research resources on large-scale bioinformatic include:

- Partner's Biobank with more than 100,000 genomic datasets (Karlson et al. 2016)
- the Million Veteran Program with 1,000,000 (Gaziano et al. 2016)
- "All of Us" with more than 1,000,000 (Denny et al. 2019)
- and the Biobank UK with 500,000 datasets for deep genetic and phenotypic data analysis (Kiryluk et al. 2019)

The "All of Us" research program uses the rich diversity in the general population to produce meaningful health outcomes research. There are also open communities that pool pharmacogenomic data and resources such as the Pharmacogene Variation Consortium (pharmvar.org), PharmGKB (pharmgkb.org), Pharmacogenomics Research Network (https://www.pgrn.org/), or the Clinical pharmacogenetics implantation consortium (cpicgx.org).

On top a patient's genetic profile, it is important to include metrics such as participant surveys, wearable technology data, food diaries, local environmental data, and repeat biosample screenings. The incorporation of psychosocial phenotypes such as catastrophizing (PCS), anxiety, depression, sleep disturbance, somatization, and social situation can also help elucidate causes behind health conditions. This, however, needs to be met with full patient participation, up-front data use policies, and proper encryption given the increasing privacy risks.

Pitfalls of Precision Medicine

While the field of personalized medicine has an exciting future, it also comes with its own challenges. To some the term itself can be misleading with somewhat arbitrary divisions. Much of the current studies only detect common variants. The relationship between genes and phenotype are not always clear as environment, exposures, and lifestyle can all influence genetic expression. Even within individuals with similar genetic and metabolic profiles, the pharmacokinetics and pharmacodynamics of medications can be variable especially considering other drug-drug interactions. Another criticism is that personalized medicine can focus on developing expensive treatments for small populations. Findings can be ambiguous and may find other genetic variants (Kiryluk et al. 2019). While the cost of genome

sequencing has gone down precipitously, it is still too cost and time prohibitive to perform point-of-care sequencing in the perioperative setting.

There are also a myriad of genes that can contribute to a single clinical metric such as the collection of genes associated with cardiac repolarization for people with long QT syndrome. With so many variants and expression profiles, it is difficult then to find individual statistical differences without clear a priori hypotheses given the statistical problem of multiple comparisons tests creating a large signal-to-noise problem.

In the two medical disciplines that represent the largest cause of morbidity—oncology and cardiology—personalized therapeutics has yet to show the hoped for salient changes in clinical outcomes. As the FDA is not able to approve use indication changes as fast as they can be detected, there are ethical issues around large scale off-label use of molecular targeting agents. The SHIVA trial compared the efficacy of molecularly targeted agents in advanced cancers, selecting patients with targetable mutations such as PI3K, AKT, mTOR, RAF/MEK with molecularly selective agents compared with conventional oncologic chemotherapy and did not show improvement in disease-free survival (Le Tourneau et al. 2015). As it stands, genome-informed therapies only help a minority of patients with advanced cancers, estimated around 7% (Marquart et al. 2018). However as our identification of new targets and therapies improve, likely so will our outcomes.

Within pain syndromes, there is an intimate, dependent relationship between the biological aspects of disease such as hyperexcitable nociceptor afferents and dysregulated neuronal circuitry with the patient's psychological state. Their experience of pain, then, is often holistically referred to using the biopsychosocial model. It is unclear how the biopsychosocial assessment will be leveraged.

Conclusion

Regional anesthesia has made large strides over the last few decades and the future stands to bring many more improvements and challenges. As our understanding of pharmacogenomics and large scale data science for interpreting clinical data improve, anesthesiologists will be able to use increasingly personalized methods for tailoring their anesthetic and within regional this can translate in many ways such as selecting the local anesthetic formulations, concentration, dose, site of injection for a specific duration, differential block, and adjuvants that would confer minimal toxicity and side effects while taking into account the patient's genetics, medical conditions, and medications.

It is conceivable that an integrated health record could indicate the best block concoction for a chosen anatomical location and duration, perhaps the site chosen based on imaging criteria of the nerve. New drugs will be developed including new local anesthetics, drugs that act on other areas of voltage-gated sodium channels, or drugs which act on other receptors such as TRPV1 in pain fibers.

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